CLINICAL STUDY PROTOCOL

Title: A Randomized Trial of Intranasal Fentanyl versus Placebo as an Adjunct to Lidocaine Infiltration in Adults undergoing Abscess Incision and Drainage in the Emergency Department

Sponsor

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Protocol Version

April 20, 2021

1 - Introduction

1.1 Introductory Statement

Incision and drainage of abscesses is one of the most painful procedures performed in US emergency departments. It has historically accounted for 2.5% of all visits and nearly 30% of procedures performed in this setting[1, 2]. The incidence of abscesses is increasing at 11% annually, more than any other ED diagnosis.[3] Delayed and inadequate treatment of pain for this and other procedures is an established and pervasive problem [4-6]. Different ED providers' analgesic practices vary with some using opioids in addition to local infiltration at the roof of the abscess or a field block.[7] There is scant literature on proper analgesia during I&D with only small trials[8] or textbooks with varying and non-consistent recommendations. [9, 10]

Opioids are effective and safe pharmaceutical agents for analgesia in an emergency setting[11, 12]. The reasons for their underutilization are multifactorial. Often providers have a tendency to underestimate the patient's level of pain compared to the patient's own perception of pain as reflected by their self-reported 0-10 Numerical Rating Scale (NRS)[13]. This is further complicated by provider discomfort in treating pain with opioids[14]. Additionally, many providers have an unfounded bias that opioid use in an emergency setting leads to long-term addiction, especially in certain socioeconomic and age groups[5, 15, 16]. It is imperative that the emergency medicine community continues to improve analgesic practice by conducting randomized clinical trials focused on pain control.

This trial will investigate the efficacy of intranasal fentanyl (INF) as an analgesic adjunct for abscess incision and drainage.

2 - Background

2.1 Background/prevalence of research topic

<u>Bioavailability and Pharmacokinetics</u>

Fentanyl is a synthetic, short-acting opioid 50-100 times more potent than morphine, with highly lipophilic properties suitable for intranasal administration. Low molecular weight, lipophilic drugs are highly conducive to rapid-transport via the nasal epithelium.[17] The efficacy may be further enhanced due to direct entrance into the CNS via the olfactory mucosa, rather than the blood brain barrier. Fentanyl's intranasal bioavailability varies between 71-89%.[17, 18] INF has an onset of action of approximately 7 (4-11 min, median) minutes and no difference in levels of pain compared to IV fentanyl up to 120 minutes (duration at least 60-120 minutes). [18, 19] Due to its pharmacokinetics and rapid-onset of action, INF will be ideal for abscess incision and drainage, a short-duration procedure.

<u>INF in post-operative setting</u>

INF has been studied in the post-operative setting.

In a randomized placebo controlled study by Veldhorst-Janssen 2010, 36 women (mean age 39.2) post-op from breast reduction where given a single dose pre-mixed solution of 0.05mg/0.1mL nasal spray fentanyl for a total mean dose of 78 mcg during drain removal. INF was more likely to afford relief than placebo.[20]

Another prospective, double-dummy, double blind RCT (n=48) in orthopedic, thyroid or abdominal surgical patients showed similar efficacy of INF compared to IV fentanyl PCA with 21/23 (91%) patients in the IN fentanyl group achieving excellent pain relief in 21 min, compared to 24/25 (96%) patients in the PCA fentanyl group in 22 min.[21]

In a single dose cross-over study of 24 gynecological patients with post-operative pain treated with IV vs INF separated by 2 hours, analgesia onset was rapid (5 min) in both groups and no difference in outcomes was found. Side-effects were not different with 4 patients in the intranasal group experiencing "nasal stinging."[19]

INF in pediatrics

INF has gained broad acceptance in pediatric emergency medicine. INF is particularly useful in pediatric patients who often require short-duration procedural analgesia and are less amenable to intravenous catheter placement.

In a randomized study, 47 pediatric patients presenting for long-bone fractures given 1mcg/kg of 50mcg/mL of INF vs 0.2mg/kg of 10mg/mL of intramuscular morphine (IMM) demonstrated fewer side effects with INF than IMM ($p<0.001$). This study also showed no difference in reduction in pain scores and no serious adverse events. One patient in the INF group required rescue analgesia.[22]

When comparing INF (1.4mcg/kg equivalent to 1mcg/kg calculated at 71% bioavailability) to intravenous morphine (0.1mg/kg) in 67 children < 18 years of age presenting to the emergency department for long bone fractures, VAS pain scores at 30 minutes decreased from 67 to 33 in the morphine group and 68 to 37 in the INF group (time=30 min difference 95% CI -4(-16 to 8)). Neither group had any cases of respiratory depression, hypotension, or decreased level of consciousness. Mean INF dose was 1.7mcg/kg due to additional doses of 15mcg, given as necessary. In the INF group 3 patients reported "bad taste" and one had an episode of vomiting 20 minutes after intervention. One patient in each group required additional doses of analgesia. [17]

In a study of 189 pediatric patients (3 to 15 years old) presenting for long bone fractures treated with 1.5mcg/kg of standard (50mcg/mL) vs high concentration (300mcg/mL) INF, both arms had substantial reduction in pain scores. Of these patients, 42(43%) in the standard concentration group required rescue medication compared with 25(28%) in the high concentration group.[17]

Fentanyl in the emergency department

The brief duration of action, potency and ease of administration, make fentanyl an optimal choice of analgesia in the emergency department. Despite this, fentanyl is used merely 10% as often as hydromorphone despite its favorable safety profile. [23]

A study by Imamoglu et al. looking at 115 adult patients receiving INF vs IV fentanyl (n=115) for renal colic, showed effective analgesia by both regimen at 15 and 30 min with rescue pain medication requirements of 55% in the IN group and 37% in the IV group (n=0.058). Adverse events occurred in 22% of patients in the IV group and only 9% in the IN group. None of these were serious.[24]

In a retrospective study of 841 patients looking at fentanyl for pre-procedural analgesia: 6 patients (0.7%) had mild side effects: nausea (1), vomiting (2), urticaria (1) and pruritis (2). Nine (1.1%) had more serious side effects including: respiratory depression (6), hypotension (3), both

hypotension and respiratory depression (1). Four of 6 of the patients who developed respiratory depression and 2 of 3 of patients who developed hypotension had alcohol levels > 160mg%. [2]
Placebo. Administration of sterile water via the intranasal route could conceivably cause analgesia through a placebo effect.[25] As an inert sterile fluid it poses no infectious or aspiration risk.

4 - Study Objectives

4.1 Hypothesis

2 mcg/kg of INF will provide better pain control than placebo when used as an adjunct to conventional local anesthesia to reduce overall pain of the procedure in adult ED patients undergoing lidocaine infiltration and subsequent abscess incision and drainage, as measured on a 0-10 pain scale.

4.2 Primary Objective

To compare the analgesic efficacy of INF to placebo as analgesic adjunct to conventional local anesthesia for the treatment of pain of the overall procedure in adult ED patients undergoing lidocaine infiltration and subsequent abscess incision and drainage, as measured on a 0-10 pain scale.

4.3 Secondary Objectives

A) To compare pain scores immediately after local analgesic infiltration and after abscess incision, instrumentation and packing
B) To compare patient satisfaction with treatment and provider perception of study medication efficacy compared to usual care
C) To compare side effect profiles and adverse events associated with the administration of INF and placebo.

5 - Study Design

5.1 General Design

This will be a randomized, double blind study of 2 mcg/kg INF versus 0.04 mL/kg IN of sterile water used adjunctively to local anesthetic in patients 18-64 years of age undergoing abscess I&D in two Montefiore EDs.

5.2 Outcome Variables

5.2.1 Primary Outcome Variables

The primary outcome is the between group difference in numerical rating scale (NRS) pain scores for overall pain of the procedure, defined as anesthetic infiltration plus abscess incision and drainage, including breaking up of adhesions, irrigation, and packing as indicated. The time for obtaining this primary NRS endpoint will be standardized as the time of completion of application of the bandage. The NRS is a reliable and validated measure of pain intensity ranging from 0 – no pain, to 10 – worst pain imaginable.

5.2.2 Secondary Outcome Variables

Secondary efficacy outcomes: difference between groups in NRS pain score immediately after infiltration with local anesthetic and difference between groups in NRS scores immediately after the completion of incision and drainage procedure, including breaking up adhesions, irrigation, and packing as indicated. Additional secondary outcomes include: patient satisfaction with treatment

described by asking "How satisfied are you with the pain medication you received for the procedure? (Satisfied, Neutral, Not Satisfied). Provider perception of treatment efficacy compared to usual care described categorically as (Better, Same, Worse). The incidence of adverse events and side effects in the two groups will be compared as will the frequency of medication use to treat side effects/adverse effects in each group.

5.3 Eligibility Criteria

Inclusion criteria

- Age 18 to 64 years of age: This is a study of adult ED patients.
- Presenting to the ED for an abscess requiring incision and drainage
- ED attending physician's judgment that the patient has capacity to provide informed consent.
- Patients must be able to understand English or Spanish.

Exclusion criteria

- Use of opioids or tramadol within past 7 days.
- Prior adverse reaction or allergy to opioids.
- Patients who are pregnant
- Patients weight > 100kg
- Chronic pain syndrome: frequently recurrent or daily pain for at least 3 months results in modulation of pain perception which is thought to be due to down-regulation of pain receptors. Examples of chronic pain syndromes include sickle cell anemia, osteoarthritis, fibromyalgia, and peripheral neuropathies.
- Medical condition that might affect metabolism or opioid analgesics such as cirrhosis (Child Pugh A or worse) or kidney impairment (CKD 3 or worse)
- Chronic malnutrition, severe hypovolemia (dehydration of blood loss) or hepatic disease
- Alcohol intoxication: history of alcoholism or the presence of alcohol intoxication as judged by the treating physician may alter pain perception and has previously increased adverse events.
- SBP <100 mmHg: Opioids can produce peripheral vasodilation causing orthostasis.
- HR < 60/min: Opioids can cause bradycardia.
- Oxygen saturation < 95% on room air: For this study, oxygen saturation must be 95% or above on room air in order to be enrolled.
- Use of MAO inhibitors in past 30 days: MAO inhibitors have been reported to intensify the effects of at least one opioid drug causing anxiety, confusion and significant respiratory depression or coma.
- Patients using transdermal pain patches or oral opioid use > 10 days in the prior month: frequent opioid use may influence both the amount of pain patients report as well as the level of relief they obtain from other treatments.
- Patients with a history of traumatic brain injury, seizures or hallucinations
- Patients with anatomical anomalies or medical conditions precluding intranasal administration

6 - Methods
6.1 Treatment - Drug
6.1.1 Identity of Investigational Product/New Drug
Fentanyl and sterile water (placebo) are both FDA approved for clinical use.

6.1.2 Dosage, Admin, Schedule (if applicable)

- Arm A: 2 mcg/kg INF, administered via intranasal route by atomizer syringe
- Arm B: 0.04ml/kg of sterile water, administered via intranasal route by atomizer syringe
    - All doses will be calculated rounding patient weight up to the nearest 10kg but not exceeding 100kg. Both arms will be given as adjuncts to local anesthetic infiltration as standard of care.

6.1.3 Method of Assignment/Randomization
Randomization will occur in blocks of four based on a random number generator.

6.1.4 Blinding
Research subjects, clinicians, and research personnel will be blinded.

6.1.5 Packaging/Labelling
The study packet will contain one item: a package containing either 4mL of fentanyl (50mcg/mL concentration = 200 mcg, the maximal dose in this weight-based study of patients <100 kg) or an identical appearing package containing 4mL sterile water

6.1.6 Storage Conditions
Study medications will be stored in the ED PYXIS at each site.

6.1.7 Concomitant therapy
Patients will receive usual care (typically local infiltration with lidocaine) as determined by the treating provider

6.1.8 Restrictions
Due to intranasal route of administration and dosing, both groups will receive no more than 4mL of intranasal solution equivalent to 200mcg of fentanyl or 4mL of sterile water

6.2 Assessments
6.2.1 Efficacy
Primary Outcome:

- The primary outcome: overall procedure NRS pain scores in each group

Secondary Outcomes:

- Baseline NRS pain scores in each group
- NRS pain scores immediately after infiltration with local analgesic
- NRS pain scores after incision, breaking of loculations, irrigation, and packing of abscess as indicated
- Difference in proportion of patients satisfied with treatment in each arm

- Difference in proportion of providers' perceived efficacy of study protocol analgesia versus standard of care
- Difference in proportion of patients who have one or more side effects in the 60 minutes post-procedure
- Incidence of adverse events between groups

Incidence of nausea, vomiting and pruritis, and adverse events will be measured and recorded at 120 minutes after the administration of intranasal medication. Pulse oximetry will be continuous and vital signs will be recorded every 15 minutes after INF administration until 120 minutes.

6.2.2 Safety

- The Research Associate will remain at the patient's bedside for the first 10 minutes after medication administration, during local infiltration and from the time of initial incision until dressing application
- At 15 minute intervals after intranasal medication administration of the study medication, the RA will measure and record vital signs (including SaO2 by pulse oximeter).
- No further monitoring will be performed after 120 minutes.

6.2.2.1 Adverse Events Definition and Reporting

Any adverse events will be managed at the discretion of the treating provider.
All vital signs that fall below the thresholds described above will be reported to the Data Safety Monitoring (DSM) individual and included in the annual progress report to the IRB. The DSM monitoring will consist of Dr. David Esses, MD, the director of the Moses ED and Dr. Polly Bijur, Ph.D, head of the Division of Research of the Department of Emergency Medicine. They will meet every month with the PI to 1) monitor adverse events and develop strategies to minimize these; and 2) monitor recruitment and enrollment.

6.3 Study Procedures

- The RAs and attending physicians will identify eligible patients. To participate, patients must have capacity to provide informed consent.
- The healthcare provider and the RA will describe the study to eligible patients and obtain patient consent.
- The RA will weigh patient, obtain a baseline NRS pain score and initial vital sign information.
- The RA will have the nurse remove the next study packet from the PYXIS, which will be either 4 ml vial containing either fentanyl 50mcg/mL or sterile water. The contents will be concealed by the research pharmacist.
- Patients will receive the blinded study medication either 2 mcg/kg of fentanyl or 0.04 mL/kg of sterile water (max 4mL) weight based and rounded to the nearest 10kg (excluding patients > 100kg to prevent excessive opioid dosing) via an atomizer syringe (half of total volume in each nostril) 15 minutes prior to local infiltration
- The RA will prompt the treating provider 15 minutes after local infiltration to ensure prompt treatment during an optimal systemic and local analgesic window. If the I&D has not been initiated within 30 minutes of INF administration the patient will not be included in the analyses due to concern for considerable tapering of INF analgesia (accounted for in sample size calculation).
- At 15 minute intervals following the intranasal medication administration, the RA will obtain vital signs (including SaO2 by pulse oximeter), and record incidence of side effects and adverse events.
- The RA will record all medications administered in the ED and the time of their administration from the chart and the treating attending physician.

- RAs will record the time of each pertinent procedural step: Initial NRS collection time, location of abscess, size of abscess (cm), complexity of procedure (simple: requires minimal blunt instrumentation, moderate: requires more than minimal blunt instrumentation, complex: requires more than moderate instrumentation), use of packing (yes/no), study medication administration time, local infiltration time, incision/instrumentation/packing /irrigation time, dressing application time and discharge time.

6.4 Statistical Method

6.4.1 Statistical Design

The statistical design is parallel group design with patients randomly allocated to the two treatments.

6.4.2 Sample Size Considerations

A sample size of 49 patients will support the primary outcome, based on the observed SD of 3.2, if the between group difference is no less than 2.8. This was calculated based on the following parameters: alpha = 0.05 and power = 0.8. Although smaller differences may be clinically relevant, a between-group difference of 2.8 is generally regarded as a robust difference.

We used nQuery Advisor version 7.0 (Los Angeles, CA) to calculate the sample size.

6.4.3 Planned Analyses

The planned analyses include: a comparison of the characteristics of the two treatment groups at baseline including NRS pain scores at baseline, immediately after infiltration with local anesthetic, immediately after abscess incision, overall NRS pain score throughout the procedure assessed at the time of dressing application. We will also compare the proportion of patients satisfied with treatment, comparison of proportion of providers' perception of efficacy of treatment compared to usual care, adverse events and side effects in the 120 minute period and graphical representation of pain over all time points.

6.4.3.1 Primary Analyses

We will calculate the NRS scores between the two treatment arms as overall procedure pain collected at the time of dressing application. An independent group t-test will be used to assess whether the NRS scores differ between the groups. Descriptive data will be calculated for all variables. The characteristics of patients in the two groups will be compared in order to confirm adequacy of randomization. If there is unequal distribution of background variables with p values of 0.15 or less, we will include them in a multivariable analysis of the outcomes.

6.4.3.2 Secondary Objectives Analyses

A similar analysis to the primary outcome analysis will be performed for NRS pain immediately after local analgesic infiltration, for NRS pain score after abscess incision and (instrumentation

and/or packing if completed) between the two treatment arms. We will calculate the difference in the proportion of patients in each group who are satisfied with treatment based upon a categorical patient-centered question answered as "Satisfied, Neutral, Not Satisfied." A chi-square test will be used to compare the proportions of patients who are satisfied with treatment. The same analyses will be done to determine provider perception of efficacy of analgesia of study medications compared to usual care.

6.4.3.3 Safety

Vital sign data and side-effects, including adverse events, will be obtained and recorded at 15 minute intervals after medication administration to ensure patient safety. Chi-square tests will be used to assess whether the proportion of patients with one or more side effects differs between treatment groups. The individual side effects will be described in tables. If there are marked differences between the distributions of background characteristics, a multi-variable regression will be performed to control for possible confounding.

6.4.3.4 Analysis of Subject Characteristics

- Background characteristics: Age, sex, race/ethnicity, initial pain intensity, nausea and vomiting before administration of analgesics. Means and standard deviations, medians and interquartile ranges, and proportions will be used to describe the sample as appropriate.

7 - Trial Administration

7.1 Ethical Considerations

Patients will not receive any compensation for their participation in this study. All data collected will be maintained within locked file cabinets or within secure databases (i.e. REDCap).

7.2 Subject Confidentiality

All data collection instruments will be secured within REDCap. The PI and co-investigators will be the only ones with access to the full database linking study IDs to patient identifying information.

7.3 Data Collection

All study data will be entered directly into REDCap by the Research Associates. Signed consent forms will be collected and kept under lock and key.

7.4 Data Safety Monitoring Plan

Data Safety Monitoring: Dr. David Esses, the director of the Moses ED and Dr. Polly Bijur, Ph.D, head of the Division of Research of the Department of Emergency Medicine, will meet monthly with the PI. This meeting will aim to 1) monitor adverse events and develop strategies to minimize these; and 2) monitor recruitment and enrollment.

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